

Trichloroethylene Issues Group

P.O. Box 68
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May 13, 1998

C.W. Jameson, Ph.D.
National Toxicology Program
Report on Carcinogens
MD EC-14
P.O. Box 12233
Research Triangle Park, N.C. 27709

RE: March 19, 1998, *Federal Register*: Report on Carcinogens, Ninth Edition

Dear Dr. Jameson:

The Trichloroethylene Issues Group is pleased to have the opportunity to comment on the 9th Report on Carcinogens. In particular we would like to address NTP's potential listing of trichloroethylene (TCE) as "reasonably anticipated to be a human carcinogen."

It is clear from the background documentation used by NTP to evaluate TCE that the agency relied heavily on animal data and much less so on the increasing epidemiological database for this chemical. First, we think NTP in general needs to find a way to better utilize epidemiological data in its risk characterization process. More specifically, we are aware of two recent epidemiological studies not addressed by NTP in its review of TCE, one conducted by industry and the other by the National Cancer Institute. We would be pleased to assist NTP staff in obtaining these if a re-evaluation of TCE is undertaken.

Our second comment deals with the need for interagency coordination prior to finalization of the NTP Annual Report. The National Center for Environmental Assessment at the U.S. Environmental Protection Agency is finishing a new toxicological assessment of TCE, as described in the two enclosed letters. This is the most comprehensive review of TCE ever undertaken, and we urge NTP to defer its decision on TCE until this document is completed. We believe the draft EPA assessment will be available to other government agencies by October of this

C.W. Jameson, Ph.D.

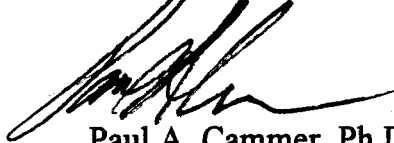
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year, and thus it makes little sense for one federal agency to finalize such a critical decision prior to the forthcoming input from another federal agency.

Please call me if you would like further information on the EPA project or if you would like assistance in obtaining the recent epidemiological data on TCE.

Sincerely,

A handwritten signature in black ink, appearing to read 'Paul A. Cammer', with a stylized flourish at the end.

Paul A. Cammer, Ph.D.
Executive Director

Enclosures



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL CENTER FOR ENVIRONMENTAL ASSESSMENT
WASHINGTON, DC 20460

OFFICE OF
RESEARCH AND DEVELOPMENT

June 12, 1996

Paul A. Cammer, Ph.D.
Trichloroethylene Issues Group
P.O. Box 68
Fairfax, VA 22039-0068

Dear Dr. Cammer:

The National Center for Environmental Assessment (NCEA) has begun to reassess the health risks associated with exposure to trichloroethylene. We would like to involve the broader scientific community in this endeavor. To assist in reaching out to scientists from all sectors, we are forming an External Involvement Group and asking you and the other individuals named in enclosure 1 to participate or nominate another scientist to serve as a member. Because of the scientific nature of the assessment activities, it is important that the individual serving on the External Involvement Group be a scientist with knowledge of trichloroethylene risk assessment issues.

Before discussing the activities of the External Involvement Group, let me describe the reassessment itself, which will look different from prior assessments. The assessment is being written in two parts. The first is a set of issue-specific state-of-the-science papers written by experts from outside EPA, many of whom are actively conducting research on trichloroethylene. We are asking these authors to present a balanced discussion of key research results, possible scientific interpretations of these results, and the strengths and limitations of the scientific information as it relates to each possible interpretation. A list of proposed topics appears in enclosure 2; we are open to other contributions and will ask the External Involvement Group to propose additional topics and secure the participation of expert authors. The second part of the assessment will be an integrative summary and EPA position, to be written by EPA staff and will draw from the state-of-the-science papers. EPA will seek comments on both parts in a public meeting, after which we will seek to publish the reassessment as a special issue of a scientific journal. The schedule for the reassessment appears in enclosure 3.

To encourage the participation of scientists from all sectors, the External Involvement Group will assist in the following functions:

1. Propose topics for additional state-of-the-science papers and secure participation of expert scientists as authors (July 1996).
2. Review recruited papers to ensure that they present a balanced and complete discussion of the state-of-the-science and do not represent advocacy positions (August-October 1996).
3. Nominate peer reviewers for the public peer review meeting that will occur in Spring/Summer 1997.
4. Keep informed the sector you are representing.

We expect these activities, except the peer review meeting, to occur through written correspondence and not require travel.

To ensure open participation, we are inviting nominations for the External Involvement Group from private industry, public interest groups, and government agencies. The individual you nominate will be expected to see that scientists from your sector have an opportunity to participate. If, for any reason, you are unable to provide a nomination for the External Involvement Group, please suggest someone else to receive this letter so that the interests of scientists in your sector will be represented.

By July 12, 1996, please send your nomination to Cheryl Siegel Scott at:

National Center for Environmental Assessment (8623)
U.S. EPA
401 M Street, SW
Washington, DC 20460
PHONE: (202) 260-5720 FAX: (202) 260-3803
INTERNET: scott.cheryl@epamail.epa.gov

We look forward to your participation in this process. By inviting participation of the broader scientific community, we hope to improve both the scientific credibility and the public acceptance of the reassessment. We thank you for your contribution in this endeavor.

Sincerely yours,



Michael Callahan
Director
National Center for Environmental
Assessment-Washington Office

Enclosure 1: Sources of Nominations

Melvin E. Andersen, Ph.D.
ICF/Crump Kaiser, Morrisville, NC

Paul A. Cammer, Ph.D.
Trichloroethylene Issues Group, Fairfax, VA

Christopher DeRosa, Ph.D.
Agency for Toxic Substances and Disease Registry, Atlanta, GA

Carol Henry, Ph.D.
US Department of Energy, Washington, DC

Phillip Landrigan, M.D., Ph.D.
Mt. Sinai School of Medicine, New York University, New York NY

Elizabeth A. Maull, Ph.D.
Department of Defense, Armstrong Laboratory, Brooks AFB, TX

Margaret Round
Northeast States for Coordinated Air Use Management (NESCAUM)
Boston, MA

Ellen Silbergeld, Ph.D.
Environmental Defense Fund, Washington, DC

Peter Voytek, Ph.D.
Halogenated Solvents Industry Alliance, Washington, DC

Lauren Zeiss, Ph.D.
California Environmental Protection Agency, Berkeley, CA

Enclosure 2: List of EPA/DOD/DOE-sponsored State-of-the Science Papers

- Development of RfC and RfD for the noncancer effects of TRI - paper will include an overview discussion of the systemic toxicity of TCE and it's metabolites. RfD's and RfC's will be developed using NOAEL/LOAEL and benchmark dose approaches.
- Cancer effects of TRI and metabolites: Human studies - an overview of the epidemiologic evidence will be presented along with insight on identifying the potential for a cancer hazard in the human population. Paper will include a discussion of recent ACGIH and IARC conclusions.
- Mode(s) of action for site-specific carcinogenic effects observed in rodents

Metabolism of TRI and it's metabolites - paper will discuss the metabolic fate and disposition of trichloroethylene, including a discussion of the metabolic pathways, oxidative and glutathione, with inferences for cross-species and high-to-low dose differences.

Mode of action of liver carcinogenicity - paper will lay out hypotheses of the roles of TCA, DCA, chloral hydrate, and metabolites produced via the glutathione pathway in the production of liver toxicity, including carcinogenicity, with an emphasis on high-to-low dose and species differences in the identified modes of action. The paper will include a discussion of the possible roles of genetic toxicity, peroxisome proliferation, and oncogene activation in liver toxicity.

Mode of action of kidney carcinogenicity - the paper will discuss the various hypotheses of the role of trichloroethylene metabolites in the production of kidney carcinogenicity and identify processes through which toxicity may be engendered. The paper will include a discussion of the genetic toxicity of metabolites and implications for kidney carcinogenicity. Species differences and similarities in metabolism and in sensitivity as well as hi-to-low-dose inferences will be part of the overall discussion.

- Pharmacokinetic models for dosimetric adjustment

Inferential ability of current models - write-up of Clewell models, with a brief discussion of past modeling efforts (Dallas, Fisher, Reitz). Dose-metrics from Clewell models will be identified for use in dose-response modeling (a separate paper, see below).

- Pharmacokinetic models for dosimetric adjustment (continued)

Future directions of physiological pharmacokinetic models - the paper will focus on the pharmacokinetic models for trichloroethylene's metabolites which are current being developed by Dr. Jeff Fisher and colleagues at Wright-Patterson Air Force Base. Dose-metrics will be identified for use in dose-response modeling (a separate paper, see below).

- Approaches for dose-response analyses - paper will set up the framework for dose-response modeling. Various dose-response approaches including biologically-based models and default approaches will be discussed. Proposed modes of action for carcinogenicity in specific target organs will be discussed in context of their support for a particular dose-response approach. Dose-response modeling will be carried out using a variety of pharmacokinetic dose surrogates.

- Uncertainty in pharmacokinetic models - paper will quantitatively examine pharmacokinetic variability and residual uncertainty in the Clewell models, using Bayesian statistical approaches, and impacts on cancer risk estimates. A second effort (yet unfunded) is to examine variability in the pharmacokinetic models of Fisher and co-workers.

Besides these papers, EPA staff will develop a biologically-based dose-response model for liver cancer, and will identify sources and pathways for exposure to trichloroethylene and selected metabolites.

STATE-OF-SCIENCE PAPERS

Jun . Jul Aug . Sep . Oct Nov . Dec

EPA	Liver MOA	O	F
	PK	F	
	PK uncertainty	O	F
	Dose-response options	O	F
	Epidemiology summary	O	F
	Exposure	O	F
AF	Metabolism	O	F
	Kidney MOA	O	F
	Future PK models	O	F
	Noncancer RfD/RfC	O	F
	Contributed papers	O	F

EPA's INTEGRATIVE SUMMARY & RISK CHARACTERIZATION . . .

Jun . Jul Aug . Sep . Oct Nov . Dec . Jan

Introduction	O	F
Hazard assessment		
-Epidemiologic summary & position	O	F
-Experimental summary & position		
-Hazard characterization		
Dose-response	O	F
-Cancer		
-Noncancer		
-Characterization		
Exposure	O	F
-Characterization		
Risk characterization	O	F
Ongoing research and data needs	O	F

NCEA will release compiled state-of-science papers and EPA position in early 1997; peer review workshop planned for Spring, 1997.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

February 4, 1997

OFFICE OF
RESEARCH AND DEVELOPMENT

Paul A. Cammer, Ph.D.
Trichloroethylene Issues Group
P.O. Box 68
Fairfax, Virginia 22039-0068

Dear Dr. Cammer:

Thank you for making time in your busy schedule to serve on the External Involvement Group for our trichloroethylene assessment. We'd like to let you know the status of the assessment and give you an opportunity to comment.

As you will recall from our letter of June 12, the assessment is being written in two parts, a set of state-of-the-science papers, followed by a synthesis and risk characterization. Since last summer, the authors have been writing their state-of-the-science papers, and we have received drafts from most of them. Enclosed for your information is a list of state-of-the-science papers comprising the first part of the assessment.

We will soon begin writing the second part of the assessment, the synthesis and risk characterization. Enclosed for your comment is an outline of the synthesis and risk characterization. It will focus on a series of hazard, dose-response, and exposure characterization issues. Please take a few minutes to look over the outline. If you would like to suggest additional issues for us to consider, please let us know by February 28.

We expect to complete a draft in the summer. Then the assessment will be reviewed and revised, starting with a review by EPA scientists and progressing to a review by an external panel of independent experts in a public meeting, hopefully, before the end of the year. We received some suggestions for peer reviewers in response to the June 12 letter. In a few months we will give you another opportunity to suggest peer reviewers. Later this year we will send you a copy of the assessment, just as soon as it is cleared for release.



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contains at least 75% recycled fiber

Enclosed you will find a fact sheet that provides more information about the trichloroethylene assessment. Please feel free to distribute the fact sheet and the outlines to your colleagues.

Thank you once again for your contributions to this endeavor. Your participation as a representative of the broader scientific community will improve both the scientific credibility and the public acceptance of the assessment. If you have any questions or comments, please call either Jim Cogliano or Cheryl Siegel Scott at 202 2603814.

Sincerely yours,



Michael Callahan
Director, Washington Office
National Center for Environmental Assessment

Enclosures

Distribution:

Melvin E. Andersen, Ph.D., ICF/Crump Kaiser
Paul A. Cammer, Ph.D., Trichloroethylene Issues Group
Christopher DeRosa, Ph.D., Agency for Toxic Substances and Disease Registry
Jodi Flaws, Ph.D., University of Maryland
Carol Henry, Ph.D., U.S. Department of Energy
Phillip Landrigan, M.D., Ph.D., Mt. Sinai Medical Center
Elizabeth A. Maull, Ph.D., U.S. Air Force
Margaret Round, Northeast States for Coordinated Air Use Management
Peter Voytek, Ph.D., Halogenated Solvents Industry Alliance
Lauren Zeise, Ph.D., California Environmental Protection Agency

HAZARD ASSESSMENT

Metabolism of trichloroethylene. Lawrence Lash and Jean Parker.

Overview of the genetic toxicity of trichloroethylene and its metabolites. Martha Moore.

Modes of action for kidney tumorigenesis. Lawrence Lash and Jean Parker.

Mode of action for liver toxicity by trichloroethylene. Richard Bull and Tony DeAngelo.

Mode of action for lung toxicity. Trevor Green.

Evaluation of the epidemiologic evidence for making inferences of cancer hazards and risks for exposure to trichloroethylene. [Author to be selected through competitive procurement].

Sensitive populations. Wendy Yap and Maria Carroquino.

DOSE-RESPONSE ASSESSMENT

Development of a physiologically based pharmacokinetic model of trichloroethylene and its metabolites for use in risk assessment. Harvey Clewell.

Physiologically based pharmacokinetic models for trichloroethylene and its oxidative metabolites in mice and humans. Jeffrey Fisher.

Dose metrics for acute neurological effects ($C \times T$ versus C). Will Boyes, Phil Bushnell, and Kevin Crofton.

Noncancer effects due to trichloroethylene: pharmacokinetics and risk assessment. Hugh Barton.

Dose-response approaches for modeling trichloroethylene carcinogenicity data. Lorenz Rhomberg.

Uncertainty associated with a pharmacokinetic model applied to a dose-response assessment of trichloroethylene carcinogenicity data. Frederic Bois.

Uncertainty associated with the Fisher et al. pharmacokinetic models applied to dose-response assessment of trichloroethylene carcinogenicity data. Frederic Bois.

Biologically based dose-response modeling. Chao Chen.

EXPOSURE ASSESSMENT

Sources, emissions, and exposure for trichloroethylene and its metabolites. Jonathan Becker.

INTRODUCTION

[Historical background, structure of this piece.]

ISSUES IN HAZARD CHARACTERIZATION

- Issue 1. What happens to trichloroethylene in the body? *[Set up the issues that follow by qualitatively identifying metabolites and target organs.]*
- Issue 2. What do the epidemiologic studies indicate about an association between trichloroethylene exposure and cancer?
- Issue 3. What do the epidemiologic studies indicate about an association between trichloroethylene exposure and other adverse effects?
- Issue 4. What do the cancer studies in laboratory animals indicate about trichloroethylene and its metabolites?
- Issue 5. What do genetic toxicity tests indicate about trichloroethylene and its metabolites?
- Issue 6. What do the mechanistic studies indicate about the relevance of these results to humans?
- Issue 7. What research could potentially resolve the open questions about the cancer hazard to humans?
- Issue 8. What do the studies in laboratory animals indicate about noncancer effects?
- Issue 9. Which noncancer effects have not been adequately studied?
- Issue 10. Considering information on potential modes of action, can highly sensitive populations be identified? *[Include statement about children.]*

ISSUES IN DOSE-RESPONSE CHARACTERIZATION

- Issue 11. Considering the pharmacokinetic modeling, which dose metrics are viable, and how should they be scaled from animals to humans?
- Issue 12. What do the pharmacokinetic studies indicate about uncertainty or variability in the dose metrics across the human population?
- Issue 13. Considering information on potential modes of action and the availability of experimental results to estimate model parameters, what are the viable approaches to cancer dose-response modeling in the observed range?

- Issue 14. What is the evidence to support either linear or nonlinear extrapolation to lower levels?
- Issue 15. How does cumulative exposure to other sources of trichloroethylene metabolites affect the risk from incremental exposure to trichloroethylene?
- Issue 16. Which approach does EPA select at this time for quantifying cancer risks from trichloroethylene?
- Issue 17. What research could potentially resolve the open questions about the cancer dose-response assessment?
- Issue 18. Considering information on dose, severity of effects, and shape of the dose-response curves, which noncancer effects are the critical effects for determining an RfD or RfC?
- Issue 19. What RfD and RfC will EPA use at this time?
- Issue 20. What research could potentially resolve the open questions about the noncancer dose-response assessment?

ISSUES IN EXPOSURE CHARACTERIZATION

- Issue 21. What are the principal sources of human exposure to trichloroethylene?
- Issue 22. What are the principal sources of human exposure to the metabolites of trichloroethylene?
- Issue 23. What are the principal pathways of human exposure to trichloroethylene and its metabolites?
- Issue 24. What can be said about different segments of the population and their levels of exposure to trichloroethylene and its metabolites?
- Issue 25. Which populations are highly exposed? *[Include statement about children.]*
- Issue 26. What research could potentially resolve the open questions about the exposure assessment?

SUMMARY OF GUIDANCE FOR RISK ASSESSORS

EXAMPLES

FACT SHEET

TRICHLOROETHYLENE HEALTH RISK ASSESSMENT

27 Jan 97

Background

Trichloroethylene (TCE) is a major contaminant of concern in EPA's air, water, and waste programs. It is found at one-third of Superfund sites. EPA's 1985 assessment and 1987 draft addendum concluded that TCE is potentially carcinogenic to humans, although in 1989 the assessment was withdrawn from IRIS (EPA's Integrated Risk Information System) pending resolution of the classification as either "possibly" or "probably" carcinogenic to humans. Since that time, new studies have provided information on how TCE causes cancer. EPA's National Center for Environmental Assessment (NCEA) is evaluating this information to update its characterization of TCE's health risks.

What will the new TCE assessment cover?

The assessment is being written in two parts. First is a set of state-of-the-science papers written by experts mostly from outside EPA, many of whom are actively conducting research on TCE. They will present a balanced discussion of key research results, plausible scientific interpretations of these results, and strengths and limitations of the scientific information supporting each plausible interpretation.

Second will be a synthesis and risk characterization, where EPA will draw from the state-of-the-science papers to update its position on TCE's health risks. Using its 1996 proposed cancer guidelines, EPA will update its position on the likelihood that TCE causes cancer. A qualitative assessment will focus on the mechanisms by which TCE causes cancer and their relevance to humans. A quantitative assessment will describe dose-response relationships, taking into account scaling from animals to humans and from high to low doses. In addition, EPA will assess the noncancer toxicity of TCE for the first time, deriving an oral reference dose (RfD) and an inhalation reference concentration (RfC).

The health risk assessment does not change EPA's standards under its air, water, or waste programs. After the assessment has been completed, EPA's regulatory programs may consider whether changes are warranted. It would be premature to speculate at this time about the likelihood, timing, or effect of any potential changes.

What provisions have been made for external peer involvement?

EPA is involving the broader scientific community in the assessment. To assist in reaching out to scientists from all sectors, an External Involvement Group, composed of representatives from private industry, public interest groups, and state and federal agencies, will assist with (1) proposing topics for state-of-the-science papers and securing expert scientists as authors, (2) reviewing these papers for balance and completeness, (3) proposing topics for the synthesis and risk characterization, (4) nominating peer reviewers, and (5) keeping scientists from their sector informed.

What provisions will be made for external peer review?

The assessment will be reviewed by a panel of independent experts at a public meeting. The meeting will be announced in the Federal Register about 4 weeks in advance. Before the review is complete, the assessment will not constitute EPA policy.

What is the schedule?

Work began on the state-of-the-science papers in early 1996, and they should be substantially complete by the middle of 1997. An external review draft, comprising the state-of-the-science papers and the synthesis and risk characterization, should be available in October, and the review meeting could take place by December. EPA will incorporate the review panel's comments into a final assessment, which, assuming a favorable review, would be issued in 1998. At that time, a summary of the assessment will be loaded onto IRIS.

How can I get a copy of the draft assessment?

When the external review draft is available, a notice will appear in the Federal Register. The draft will be available on the WorldWide Web, or copies can be purchased from the National Technical Information Service (NTIS).

Whom can I call for more information?

You can call either Jim Cogliano or Cheryl Siegel Scott at 202 260-3814. This fact sheet will be updated as the information it contains changes.